Restoring function in exhausted CD8 T cells during chronic viral infection

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Abstract

Functional impairment of antigen-specific T cells is a defining characteristic of many chronic infections, but the underlying mechanisms of T-cell dysfunction are not well understood. To address this question, we analyzed genes expressed in functionally impaired virus-specific CD8 T cells present in mice chronically infected with lymphocytic choriomeningitis virus (LCMV), and compared these with the gene profile of functional memory CD8 T cells. Here we report that PD-1 (programmed death 1; also known as Pdcd1) was selectively upregulated by the exhausted T cells, and that in vivo administration of antibodies that blocked the interaction of this inhibitory receptor with its ligand, PD-L1 (also known as B7-H1), enhanced T-cell responses. Notably, we found that even in persistently infected mice that were lacking CD4 T-cell help, blockade of the PD-1/PD-L1 inhibitory pathway had a beneficial effect on the 'helpless' CD8 T cells, restoring their ability to undergo proliferation, secrete cytokines, kill infected cells and decrease viral load. Blockade of the CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) inhibitory pathway had no effect on either T-cell function or viral control. These studies identify a specific mechanism of T-cell exhaustion and define a potentially effective immunological strategy for the treatment of chronic viral infections.